Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Summary of Pre-treatment Dosing Recommendations

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Impact of *DPYD* Variants on DPD Enzyme Activity

Table 1 – Reduction in DPD activity associated with *DPYD* variants

DPYD Variant	Activity Score[a]	Functional Status[b,7]	Reduction in DPD Activity	
			Heterozygous State[7,9,16,17]	Homozygous State[9]
Wild type e.g. c.1627A>G (*5) c.85T>C (*9A)	1	Normal activity	None	None
c.2846A>T	0.5	Decreased activity	30%	50%
c.1236G>A, c.1129-5923C>G[c] haplotype B3 (HapB3)	0.5	Decreased activity	35%	20-70%
c.557A>G	0.5	Decreased activity	46%	N/A
c.2279C>T	0.5	Decreased activity	45%[d]	N/A
c.868A>G	0.5	Decreased activity	45%[d]	N/A
c.1905+1G>A (*2A)	0	No activity	50%	100%
c.1679T>G (*13)	0	No activity	68%	75%

N/A Not available

a Individual variant allele activity score (distinct from gene activity score); see Appendix 2 in the full guideline for definitions

b Variant allele definitions and assignment of allele function can be found in the CPIC DPYD Allele Functionality Table[18]

c Recent evidence suggests that these 2 variants are not in complete linkage disequilibrium (one may exist without the other); c.1129-5923C>G is likely the causal variant leading to decreased function.

d Heterozygous expression in vitro. There is currently no clinical data available for DPYD variants c.2279C>T and c.868A>G.

Pharmacogenomic-Guided Dosing Recommendations

Table 2 – Fluoropyrimidine Starting Dose Recommendations by DPYD Variant

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
Homozygous	any normal function variant	any normal function variant	2	Normal	No dose adjustment
	c.1905+1G>A (*2A)	c.1905+1G>A (*2A)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
	c.1679T>G (*13)	c.1679T>G (*13)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
	c.1129-5923C>G, c.1236G>A (HapB3)	c.1129-5923C>G, c.1236G>A (HapB3)	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%[e]
	c.557A>G	c.557A>G	1	Intermediate	Reduce[d] starting dose by at least 50%
	c.2279C>T	c.2279C>T	1	Intermediate	Reduce[d] starting dose by at least 50%
	c.868A>G	c.868A>G	1	Intermediate	Reduce[d] starting dose by at least 50%
Heterozygous	c.1905+1G>A (*2A)	any normal function variant	1	Intermediate	Reduce[d] starting dose by 50%
	c.1679T>G (*13)	any normal function variant	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 50%
	c.2279C>T	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 25-50%
	c.868A>G	any normal function variant	1.5	Intermediate	Reduce[d] starting dose by 25-50%

Refer to the "Fluoropyrimidine Treatment in Patients with Dihydropyrimidine Dehydrogenase (DPD) Deficiency: Guidance for Clinicians" for more information, including references and limitations of DPYD testing.

Please note: Recommendations are based on data largely derived from individuals of European ancestry. Current testing does not identify all DPYD variants and may not assess other rare, clinically relevant variants that have yet to be identified or for which association with enzyme activity have not yet been established. Clinical judgement should be exercised when interpreting results, especially in racial/ethnic or ancestral groups that have not been studied as extensively.

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
Compound Heterozygous	c.1905+1G>A (*2A)	c.1679T>G (*13)	0	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens.
	c.1905+1G>A (*2A)	c.1129-5923C>G, c.1236G>A (HapB3)	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1905+1G>A (*2A)	c.2846A>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1905+1G>A (*2A)	c.557A>G	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1905+1G>A (*2A)	c.2279C>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
	c.1905+1G>A (*2A)	c.868A>G	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1679T>G (*13)	c.1129-5923C>G, c.1236G>A (HapB3)	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1679T>G (*13)	c.2846A>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1679T>G (*13)	c.557A>G	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1679T>G (*13)	c.2279C>T	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring

Status	*DPYD* Variant 1	*DPYD* Variant 2	Activity Score[a]	*DPYD* Metabolizer[b]	Starting Dose Recommendation[c]
	c.1679T>G (*13)	c.868A>G	0.5	Poor	Avoid use of 5-FU or 5-FU prodrug-based regimens. If alternative agents are not considered a suitable therapeutic option, 5-FU should be administered at a strongly reduced dose (by > 75%) with toxicity monitoring
	c.1129-5923C>G, c.1236G>A (HapB3)	c.2846A>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	c.557A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.1129-5923C>G, c.1236G>A (HapB3)	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.557A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.2846A>T	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	c.2279C>T	1	Intermediate	Reduce[d] starting dose by 50%
	c.557A>G	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%
	c.2279C>T	c.868A>G	1	Intermediate	Reduce[d] starting dose by 50%

a. Activity score is calculated as the sum of the two individual variant allele activity scores (1=fully functional, 0.5=reduced function, and 0=non-functional).
b. Likely phenotype: extent to which the variant alleles influence enzyme activity
c. For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.
d. Followed by titration of dose based on tolerability. Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.
e. May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports

Adapted from the 2017 CPIC Guidelines and Supplementary Tables. CPIC guidelines and content are subject to updates and modifications, refer to cpicpgx.org for most current content.

Table 3 & 4: Fluoropyrimidine Starting Dose Recommendations Summary[a]

Table 3 - Fluoropyrimidine Starting Dose Recommendations for DPYD Variants in the Heterozygous State[a]

DPYD Variant (Heterozygous[a])	Starting Dose Recommendation[b]
c.1905+1G>A (*2A)	Reduce[c] starting dose by 50%
c.1679T>G (*13)	Reduce[c] starting dose by 50%
c.1129-5923C>G, c.1236G>A (HapB3)	Reduce[c] starting dose by 50%
c.2846A>T	Reduce[c] starting dose by 50%
c.557A>G	Reduce[c] starting dose by 50%
c.2279C>T	Reduce[c] starting dose by 25-50%
c.868A>G	Reduce[c] starting dose by 25-50%

Table 4 - Fluoropyrimidine Starting Dose Recommendations for DPYD Variants in the Homozygous State:

DPYD Variant (Homozygous)	Starting Dose Recommendation[b]
c.1905+1G>A (*2A)	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1679T>G (*13)	Avoid use of 5-FU or 5-FU prodrug-based regimens.
c.1129-5923C>G, c.1236G>A (HapB3)	Reduce[c] starting dose by 50%
c.2846A>T	Reduce[c] starting dose by 50%[d]
c.557A>G	Reduce[c] starting dose by at least 50%
c.2279C>T	Reduce[c] starting dose by at least 50%
c.868A>G	Reduce[c] starting dose by at least 50%

a. Not including compound or double heterozygous.
b. For standard dosing of 5-FU or capecitabine. Excludes low (metronomic) dosing as this was not represented in studies; dose adjustments in these patients should be based on clinical judgement.
c. Followed by titration of dose based on toxicity. Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities.
d. May require > 50% dose reduction in starting dose for carriers of this genotype, based on case reports

Adapted from the 2017 CPIC Guidelines and Supplementary Tables. CPIC guidelines and content are subject to updates and modifications, refer to cpicpgx.org for most current content.